# Early Diagnosis and Treatment of Rheumatoid Arthritis

Emily A. Littlejohn, DO[a], Seetha U. Monrad, MD[b,*]

**KEYWORDS**

• Rheumatoid arthritis • Synovitis • Extra-articular manifestations • Diagnostic criteria
• Disease-modifying antirheumatic drugs • Biologic agents

**KEY POINTS**

- Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder that primarily targets synovial joints, resulting in synovitis, synovial hypertrophy, cartilage and bone destruction, autoantibody production, and systemic symptoms.
- RA classically presents as a symmetric inflammatory polyarthritis involving the hands, wrists, and feet; however, there are several important extra-articular manifestations.
- The 2010 diagnostic criteria emphasize early identification of patients with RA to facilitate early treatment, which results in improved outcomes.
- Pharmacologic treatment involves combinations of anti-inflammatory agents, disease-modifying antirheumatic drugs, and biologic therapies.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily targets synovial joints, resulting in pain and functional limitations. It is the most common inflammatory arthritis, and a significant cause of morbidity and mortality. From the primary care perspective, early recognition of this disease, along with its extra-articular manifestations, can lead to faster time to treatment and better health outcomes, in addition to preserved joint functionality.

## EPIDEMIOLOGY

Worldwide, the prevalence of RA is believed to range from 0.4% to 1.3%.[1,2] In 2005, an estimated 1.5 million, or 0.6%, of US adults 18 years or older had RA.[3] According to

[a] Rheumatologic and Immunologic Diseases, Cleveland Clinic, Orthopaedic and Rheumatologic Institute, 9500 Euclid Avenue/A50, Cleveland, OH 44195, USA; [b] Division of Rheumatology, Michigan Medicine, 7D08 North Ingalls Building, 300 North Ingalls Street, Ann Arbor, MI 48109, USA
* Corresponding author.
*E-mail address:* seetha@med.umich.edu

Prim Care Clin Office Pract 45 (2018) 237–255
https://doi.org/10.1016/j.pop.2018.02.010
primarycare.theclinics.com

the most recent data from the Rochester Epidemiology Project,[3] 41 per 100,000 people were diagnosed with RA annually between 1995 and 2007. Although RA can occur in patients at any age, incidence was found to rise with age; among those aged 18 to 34, 8.7 per 100,000 people were affected; in those aged 65 to 74 years, 89 per 100,000 were affected; and in those 85 years or older, 54 per 100,000 were affected. This study cohort estimated the lifetime risk of RA to be 4% among women and 3% among men.[4]

Given increasing life expectancies worldwide, the number of elderly people with RA is growing.[5] This is important, as therapeutic goals differ according to patient age or presence of risk factors for infection,[5] something that both primary care physicians and rheumatologists should be continually monitoring.

From a public health perspective, people with RA have been found to be significantly more likely to have reduced their work hours or stopped working; they are more likely to have lost their job or to have retired early; and are 3 times more likely to have had a reduction in household family income than either individuals with osteoarthritis (OA) or those without arthritis.[6] In this way, the economic effects of RA are staggering and emphasize the importance of early recognition and treatment.

## RISK FACTORS

Although the exact cause of RA is unknown, it is generally accepted that multiple factors likely interact in a genetically susceptible host. Studies suggest that heritability is approximately 65%.[7] Genes within the HLA locus, particularly HLA-DRB1, account for just under half of the genetic component of susceptibility,[8] in addition to being associated with increased disease severity.[9] From a gender perspective, women are 2 to 3 times more likely to develop RA than men. It has been postulated this is in part due to the stimulatory effects of estrogen on the immune system.[10,11] Studies have been largely mixed with regard to pregnancy and the risk of RA development, although show a trend toward a protective effect.[12]

Known risk factors for the development of RA include smoking, obesity, and periodontal disease; the gut microbiome and infections also have been implicated. Smoking confers significant risk for the presence of anti-citrullinated protein antibodies (ACPA or anti-CCP), which are important diagnostic and prognostic markers in RA; the risk is amplified in the presence of specific HLA-DRB1 alleles.[13] This is thought to be due to the immunomodulatory effects of smoking, including decreased phagocytic and antibacterial functions of alveolar macrophages, shifts in cytokine production, and oxidative stress.[13] In addition to its effect on susceptibility, cigarette smoking also may be a risk factor for greater disease severity.[14] Although results are mixed, large epidemiologic studies suggest that obesity may be associated with a modestly increased risk for the development of RA.[15] Other studies have shown that obesity is generally associated with worse subjective measures of disease activity, which may be confounded by osteoarthritis, disability, and chronic pain.[15]

The association between oral disease/periodontitis and RA has been recognized since the early 1800s, with the most rudimentary treatment consisting of tooth extraction. Many large epidemiologic studies and smaller case-control and cohort studies have shown an association between periodontal disease and RA with odds ratios ranging 1.8:1 (95% confidence interval [CI] 1.0–3.2, NS) to 8:1 (95% CI 2.9–22.1, $P<.001$).[16] An emerging body of evidence has outlined periodontal health and its association with RA through the common periodontal microbe *Porphyromonas gingivalis*. The specific abilities of *P gingivalis* to citrullinate host peptides can induce autoimmune responses in RA through development of anti-CCP antibodies.[17] The unique interplay between the gut microbiome and functions of the host immune